PROCESS FOR THE MANUFACTURE OF N-ALKOXALYL-ALANINATES

The present invention relates to a process useful in the multistep process for the manufacture of vitamin B_6. More particularly, the present invention relates to a process for the manufacture of alkyl N-alkoxalyl-alaninates, i.e. compounds which may be represented structurally as alkylO-CO-CO-NH-CH(CH_3)-CO-Oalkyl and which are useful intermediates in the multistep process. Furthermore, the invention also relates to novel intermediates generated in the process of the present invention, i.e. certain N-alkoxalyl-alanines, being monoesters corresponding to the aforementioned alaninates and which may be represented structurally as alkylO-CO-CO-NH-CH(CH_3)-COOH.

There have been numerous publications on the synthesis of alkyl N-alkoxalyl-alaninates. One such approach, as described in Chem. Ber. 30, 579 (1897) and Bull. Chem. Soc. Japan 42(5), 1435-1457 (1969), and the patent publications French Patent No. 1,533,817 and Japanese Patent No. 43.010,614 (B4; 1968), involves the reaction of an alkyl alaninate as such or as its hydrochloride with an alkoxalyl chloride or a dialkyl oxalate optionally in the presence of a base, e.g. trialkylamine, and/or in the presence of an alkanol, e.g. ethanol. In none of these cases is alanine itself reacted.

A further known approach involves the synthesis of alkyl N-alkoxalyl-alaninates directly from alanine as the free acid. Thus French Patent Publication (Application) No. 2,010,601, Japanese Patent No. 46.002,969 (1971) and Bull. Chem. Soc. Japan 45, 1917-1918 (1972) describe the reaction of alanine itself with oxalic acid in the presence of an alkanol, particularly methanol or ethanol, to produce the appropriate alkyl N-alkoxalyl-alaninate. The alkyl (ethyl) N-formyl alaninate was produced as a by-product in up to 10% yield under these conditions. The authors of the Bull. Chem. Soc. Japan reference disclose a modified approach which minimizes the formation of said by-product to trace levels by reacting alanine with oxalic acid and both alkanol (ethanol) and dialkyl (diethyl) oxalate.

A still further approach, using acidic conditions, is disclosed in the Chinese Patent Publication No. 86101512A and in Zhongguo Yiyao Gongye Zazhi 25(9), 385-389 (1994) of H. Zhou et al. Here, alanine is reacted with oxalic acid in an aqueous hydrogen chloride-ethanol solvent mixture with azeotropic removal of the formed water using benzene to afford ethyl N-ethoxalyl-alaninate, and addition of diethyl oxalate and anhydrous sodium carbonate to the crude ester product. The required multistep work-up is complicated and thus a disadvantage in this particular approach.

Finally, German Offenlegungsschrift (DOS) No. 4,015,255 describes inter alia mono- and diesters of N-oxalyl-alanine as medicaments, refers to French Patent Publication No. 2,010,601 (see above) for the synthesis of such mono-and diesters and exemplifies the preparation of the diesters generally by reacting "alanine ester hydrochloride" with "oxalic ester chloride" in methylene chloride as the solvent in the presence of a mixture of triethylamine and N,N-dimethylaminopyridine as the base. Although the diesters and also N-alkoxalyl-alanines (monoesters) are claimed as medicaments, and the synthesis of methyl N-methoxalyl-alanine, named as "(N-oxalyl)-L-alanine dimethyl ester", is actually exemplified in the pertinent Example 1, there is no specific disclosure/example of the synthesis of N-alkoxalyl-alanines such as N-ethoxalyl-alanine.

The process of the present invention enables the manufacture of alkyl N-alkoxalyl-alaninates from alanine itself in high yield while avoiding the drawbacks inherent to known processes. In particular, the process of the present invention avoids the generation of large amounts of inorganic salt waste normally encountered in the known acid catalyzed processes for the manufacture of these alaninates.

Thus, as one aspect, the present invention provides a process for the manufacture of alkyl N-alkoxalyl-alaninates which comprises reacting alanine with a dialkyl, preferably a di(lower alkyl), oxalate under substantially non-acidic conditions.

The term alanine as used herein comprises racemic (D,L)-alanine as well as the individual enantiomers L- and D-alanine and mixtures of both enantiomers in any ratio.

The di(lower alkyl) oxalate features in particular C_{1-8}-alkyl groups, preferably C_{1-4}-alkyl groups, which when containing 3 or more carbon atoms may be straight chain or branched. These dialkyl oxalates are in many cases known compounds which are

commercially available. Any novel ones may be produced by methods analogous to the known methods, e.g. by conventional esterification of oxalic acid with the appropriate alkanol using an acid catalyst, e.g. sulphuric acid.

That the reaction is carried out under substantially non-acidic conditions means that apart from alanine [H_2N-CH(CH_3)-COOH] itself no further acid is present in the reaction mixture, so that no acid apart from alanine is deliberately added or otherwise included in the reaction mixture. To create such substantially non-acidic conditions, however, a base may be included in the reaction mixture. In a preferred aspect, the reaction is carried out without the presence of an added base in the reaction mixture. If however a base is present, said base is suitably an organic base, in particularly a trialkylamine; a cyclic tertiary amine (including a base of the type heteroaromatic compound), such as pyridine, quinoline (both also examples of heteroaromatic compounds), N-methyl-pyrrolidine or N-methyl-piperidine; or a cyclic tertiary amide, such as N-methyl-pyrrolidone; or any mixture of two or more of such bases. The term "alkyl" as used in trialkylamine refers to straight chain or branched alkyl groups containing 1-8, preferably 1-4, carbon atoms. The most preferred types of bases, i.e. those which promote the best yields of alkyl N-alkoxalyl-alaninates, are trialkylamines, triethylamine and tripropylamine being particularly preferred. Of the cyclic tertiary amines N-methyl-pyrrolidine and N-methyl-piperidine are preferred. In general a low boiling base, i.e. a base having a boiling point at atmospheric pressure which is substantially below about 135°C, is preferably used.

In the reaction mixture of the alanine and the dialkyl oxalate the latter reactant is preferably in excess molar amount. More particularly, the molar ratio of alanine to dialkyl oxalate is suitably from about 1 : 2 to about 1 : 10, preferably from about 1 : 3 to about 1 : 6, and most preferably about 1 : 4.

When a base is used, the molar ratio of base to the reactant which is used in the lesser molar amount, usually, as indicated above, the alanine, is suitably from about 0.25 : 1 to about 2 : 1, preferably from about 1 : 1 to about 1.5 : 1. Expressed in terms of mol% the amount of base used is suitably from about 25 mol% to about 200 mol%, preferably from about 100 mol% to about 150 mol%, of the amount of that reactant.

The temperatures at which the process of the present invention is suitably carried out depend, amongst other factors, on whether an added base is present in the reaction

mixture or not, and are generally in a higher range when no base is present. In the latter case the reaction is suitably carried out at a temperature from about 120°C to about 200°C, preferably from about 135°C to about 160°C. In the other case, i.e. when a base is present, the reaction is suitably carried out at a temperature from about 60°C to about 160°C, preferably from about 80°C to about 120°C, and most preferably from about 90°C to about 110°C.

The reaction of the alanine with the dialkyl oxalate central to the process of the present invention apparently proceeds by a mechanism which involves an initial formation of the appropriate N-alkoxalyl-alanine of the formula alkylO-CO-CO-NH-CH(CH_3)-COOH with release of the appropriate alkanol, followed by the involvement of the generated alkanol in the esterification of said N-alkoxalyl-alanine to the desired alkyl N-alkoxalyl-alaninate of the formula alkylO-CO-CO-NH-CH(CH_3)-CO-Oalkyl. Accordingly, it is appropriate either to perform the reaction under temperature and pressure conditions which ensure minimal loss of the pertinent generated alkanol, or to perform the reaction with added alkanol.

Thus in one embodiment of the process of the present invention, the reaction is carried out in such a way as to ensure that as much as possible of the alkanol produced during the reaction remains in the reaction system either by carrying out the reaction under atmospheric pressure with cooling of the vapour phase of the reaction mixture to promote the return of the alkanol into the reaction system, or by carrying out the reaction at elevated pressure in a closed system, e.g. in an autoclave. In both cases it is clearly unnecessary to carry out of the reaction in the presence of added alkanol.

In an alternative embodiment of the process of the present invention the reaction is carried out in the presence of added alkanol, preferably alkanol featuring the alkyl group corresponding to that of the employed dialkyl oxalate. In this case the reaction can be performed at atmospheric pressure and a certain loss of alkanol from the reaction system can be tolerated.

When an alkanol is used, the molar ratio of alkanol to the reactant which is used in the lesser molar amount, usually, as indicated above, the alanine, is suitably from about 1 : 1 to about 10 : 1, preferably from about 3 : 1 to about 6 : 1.

If the reaction is carried out under atmospheric pressure in the presence of an organic base the reaction is suitably performed by initially heating the reaction mixture for about 4 to about 12 hours, preferably for about 6 to about 10 hours, to a temperature below the boiling point of the organic base. As indicated above, the temperature during heating is then suitably from about 60°C to about 160°C, preferably from about 80°C to about 120°C, most preferably from about 90°C to about 110°C, and furthermore a low boiling base, i.e. a base having a boiling point substantially below about 135°C under atmospheric pressure, is preferably used. During this initial heating period the base should be retained in the reaction mixture, and if necessary precautions taken, e.g. the use of condensation means (reflux reaction), to ensure this. Thereafter, any low boiling organic base is suitably removed from the reaction mixture, e.g. by distillation, and the temperature of the reaction mixture then increased up to about 160°C for a duration sufficient to complete the formation of the desired diester product, i.e. the alkyl N-alkoxalyl-alaninate. This final heating step for the formation of the desired diester product is usually completed in about 4 to 12 hours, preferably about 6 to 10 hours.

As indicated above, the process of the present invention apparently proceeds via the appropriate N-alkoxalyl-alanine, of the formula alkylO-CO-CO-NH-CH(CH_3)-COOH, e.g. N-ethoxalyl-alanine in the case where the alkyl group is ethyl. These compounds are novel and as such are also an object of the present invention. If not intermediates in the process according to the present invention and thus anyway converted into the appropriate alkyl N-alkoxalyl-alaninates as described above, the isolated N-alkoxalyl-alanines can be readily so converted by heating in the presence of a dialkyl oxalate such as diethyl oxalate, and the produced alkyl N-alkoxalyl-alaninate can subsequently be isolated from the reaction mixture. Thus, the process of the present invention can be carried out with or without isolation of the N-alkoxalyl-alanine intermediate, and if said isolation is desired the reaction conditions can be adjusted appropriately to promote an optimal generation of the intermediate for subsequent isolation. When a "one-pot" synthesis of alkyl N-alkoxalyl-alaninate is performed using triethylamine as the added base, for example, the N-alkoxalyl-alanine is generated as the major product after an initial heating period, and so these conditions may suitably be used to produce and isolate the novel N-alkoxalyl-alanine in a major quantity. In an alternative embodiment the process is carried out without a base and with the removal of the alkanol and water generated during the initial heating period, thereby forming the desired N-alkoxalyl-alanine as the major product. Said product, e.g. N-ethoxalyl-alanine, can then be isolated from the mixture in the reaction vessel by column chromatography over silica gel, for example, or more preferably by crystallization.

A so-obtained alkyl N-alkoxyoxalyl alaninate can be converted by known methods into vitamin B_6, e.g. by cyclization to form the appropriate 4-methyl-5-alkoxy-2-alkoxycarbonyl-oxazole which on treatment with alkali and subsequently acid can be converted into the appropriate 4-methyl-5-alkoxy-oxazole. The latter, on reaction with a 2-unsubstituted, 2-monosubstituted or 2,2-disubstituted 4,7-dihydro-(1,3)-dioxepin such as 2-isopropyl-4,7-dihydro-(1,3)-dioxepin can be further converted into vitamin B_6, as disclosed for example in French Patent No. 1,533,817, U. S. Patents Nos. 3,250,778, 3,296,275 and 3,822,274, and Indian Patent No. 175,617.

The process of the present invention is illustrated by the following Examples:

Example 1

17.9 g, (200 mmol) of D,L-alanine followed by 24.4 g (33.4 ml, 240 mmol, 1.2 equivalents) of triethylamine and finally 117.5 g (800 mmol, 4 equivalents) of diethyl oxalate were introduced into a reaction flask under a stream of argon. A gas trap containing 100 ml of a 10% aqueous solution of barium chloride was connected to the gas outlet of the reaction flask in order to trap any carbon dioxide produced during the reaction. The reaction mixture was heated at 105°C (internal temperature) for 8 hours (after 6 hours all the alanine was in solution). Analysis by gas chromatography (hereinafter "GC", performed in this and each further case at this stage on a silica gel column of dimensions 30 m x 0.28 micron showed 1.2 w/w % of ethyl N-ethoxalyl-alaninate (hereinafter "EOAE") and 22.3 w/w % of N-ethoxalyl-alanine (hereinafter "EOA") as the major products (98.4% yield based on the employed amount of alanine) at this stage in the reaction sequence. No carbon dioxide production was observed during the first heating phase. The reaction mixture was then heated up to 145°C over 30 minutes and maintained at this temperature for a further 8 hours. During this second heating period triethylamine and ethanol were removed by distillation into a collector. In the second heating period, production of carbon dioxide occurred and a precipitate of barium carbonate was observed in the gas trap. GC analysis of the mixture at the end of the reaction showed EOAE produced as the major product in 28.7 w/w % amount with some EOA remaining in 2.2 w/w % amount. The overall yield of EOAE + EOA in this two-step, one-pot process, calculated from the employed amount of alanine, was 73.9%.

Example 2

To a stainless steel autoclave under an argon atmosphere there were added 0.9 g (10 mmol) of D,L-alanine followed by 1.2 g (1.7 ml, 12 mmol, 1.2 equivalents) of triethylamine and 5.9 g (40 mmol, 4 equivalents) of diethyl oxalate. The reaction mixture was heated at 150°C (heating block temperature) for 8 hours. The internal pressure following the reaction was about 5 bar (0.5 MPa). The autoclave was then allowed to cool over 15 minutes and a sample of the resulting brownish mixture was removed for GC analysis. The mixture contained EOAE as the major product in 22.0 w/w % amount and some EOA in 0.5 w/w % amount. The overall yield of EOAE + EOA based on the employed amount of alanine was 79.2%.

Example 3

8.9 g (100 mmol) of D,L-alanine followed by 58.8 g (400 mmol, 4 equivalents) of diethyl oxalate were introduced into a reaction flask under a stream of argon. A gas trap containing 100 ml of a 10% aqueous solution of barium chloride was connected to the gas outlet of the reaction flask in order to trap any carbon dioxide produced during the reaction. The reaction mixture was heated at 145°C (internal temperature) for 7 hours (after 6 hours all the alanine was in solution). GC analysis of the mixture at the end of the reaction showed EOAE produced in 12.5 w/w % amount with EOA remaining as the major product in 16.0 w/w % amount. The overall yield of EOAE + EOA in this two-step, one-pot process, calculated from the employed amount of alanine, was 95.0%.

Example 4

To a stainless steel autoclave under an argon atmosphere were added 2.23 g (25 mmol) of D,L-alanine followed by 14.69 g (100 mmol, 4 equivalents) of diethyl oxalate. The reaction mixture was heated at 150°C (heating block temperature) for 8 hours. The internal pressure following the reaction was about 5 bar (0.5 MPa). The autoclave was then allowed to cool over 15 minutes. The unreacted alanine (1.5 g, 17.3 mmol) was removed by filtration, amounting to a recovery of 69.1%, and a sample of the residual light brown mixture was removed for GC analysis. The reaction mixture contained EOAE in 1.0 w/w % amount and EOA in 3.0 w/w % amount as the major product. The overall yield of EOAE + EOA based on the employed amount of alanine was 26.5%, and the corrected yield of the reaction based on the recovery of the unreacted alanine was 95.6%.

Example 5

Into a double-jacketed, 4-necked 500 ml glass reactor equipped with a circulation thermostatic temperature control, an overhead stirrer with propeller, a thermometer/ controller, a dephlegmator (partial condensation head), a reflux cooler, a vacuum system, cold traps and argon degassing means were introduced under an argon atmosphere 44.7 g (500 mmol) of D,L-alanine followed by 298.6 g (2 mol, 4 equivalents) of diethyl oxalate. The suspension was stirred at 200 rpm and was heated for one hour up to an internal temperature of 145°C (mantle temperature 150°C). At the start of the reaction the dephlegmator was set to 5°C. Alanine was completely dissolved after about 6 hours reaction time. During the course of the reaction, the internal temperature dropped from 145°C to 115°C. After a further 26 hours the dephlegmator was heated to 70°C and ethanol and other low boiling constituents were distilled off from the reaction mixture over 30 minutes at an internal temperature of 116°C and a reduced pressure from 0.9 bar to 0.4 bar ((90 kPa to 40 kPa) into a prefraction collecting flask. The collecting flask was changed and the dephlegmator heated to 110°C. The unreacted excess diethyl oxalate was distilled off from the reaction products over a period of 2 hours at an internal temperature from 116°C to 154°C and a reduced pressure from 400 mbar to 40 mbar (40 kPa to 4 kPa). The resulting mixture containing the crude desired product was cooled to room temperature, analyzed by GC, and found to contain 77.0 w/w % of EOAE and 5.5 w/w % of EOA. The overall yield of EOAE + EOA based on the employed amount of alanine was 75.0%.

Example 6

0.9 g (10 mmol) of D,L-alanine followed by 1.8 g (2.3 ml, 40 mmol, 4 equivalents) of ethanol and 5.9 g (40 mmol, 4 equivalents) of diethyl oxalate were added to a stainless steel autoclave under an argon atmosphere. The reaction mixture was heated at 150°C (heating block temperature) for 8 hours. The internal pressure following the reaction was about 5 bar (0.5 MPa). The autoclave was allowed to cool over 15 minutes, and a sample of the resulting pale yellow mixture was removed for GC analysis. The reaction mixture contained EOAE as the major product in 18.5 w/w % amount and some EOA in 1.7 w/w % amount. The overall yield EOAE + EOA based on the employed amount of alanine was 78.4%.

Example 7

8.9 g (100 mmol) of alanine followed by 12.2 g (8.9 ml, 120 mmol, 1.2 equivalents) of triethylamine and 59.7 g (400 mmol, 4 equivalents) of diethyl oxalate were introduced

into a reaction flask under an atmosphere of argon, and the reaction mixture was heated at 100°C for 7 hours. The mixture was cooled to 2-3°C and stirred a further 2 hours. The unreacted alanine that precipitated from the reaction mixture was isolated by filtration over a membrane filter (cellulose, 0.45 microns). The triethylamine was first removed by rotary evaporation at 20 mbar (2 kPa) and 60°C, and then the excess diethyl oxalate was removed under high vacuum rotary evaporation at 0.01 mbar (1 Pa) and 70°C. The remaining crude product (14.5 g), a yellowish gold oil, was analysed by GC. EOA was found as the major product in 80.2 w/w % amount, corresponding to a yield based on the employed amount of alanine of 62%. For the isolation and characterization of the EOA the crude product was purified by column chromatography over silica gel (0.040-0.063 mm), ethyl acetate/acetonitrile (EtOAc/CH_3CN) 8 : 2 v/v, 2% acetic acid (AcOH), column size 8 x 20 cm] to yield 1.0 g of pure EOA (> 99 w/w %) as an off-white solid. The structure of the isolated EOA was characterized as below.

Analysis:

R_f (silica gel, EtOAc/CH_3CN 8:2 v/v, 2 % AcOH) = 0.30;

Melting point = 73-74°C (uncorrected);

^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.28 (t, J = 7.0 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.34 (d, J = 7.2 Hz, 3 H, CH_3), 4.24 (q, J = 7.0 Hz, 2 H, $OC\underline{H}_2CH_3$), 4.26 (dq, J = 7.6, 7.2 Hz, 1 H, $NHC\underline{H}CH_3$), 9.02 (d, J = 7.6 Hz, 1 H, $CONH\underline{C}H$), 12.70 (bs, 1 H, COOH);

^{13}C-NMR (100 MHz, DMSO-d_6): δ (ppm) = 13.8, 16.5, 47.9, 62.0, 156.9, 160.5, 172.9;

IR (KBr): ν = 3365, 3126, 3006, 1733, 1664, 1539, 1278, 1193 cm^{-1};

Mass spectroscopy (elec. spray, negative mode): 188.2 $(M- H^+)^-$;

Elemental analysis for $C_7H_{11}NO_5$ (189.17): calculated C 44.45, H 5.86, N 7.40%; found C 44.20, H 5.78, N 7.11%.

Example 8

5.93 g (66 mmol) of alanine followed by 8.08 g (11.13 ml, 80 mmol, 1.2 equivalents) of triethylamine and finally 39.8 g (37 ml, 240 mmol, 4 equivalents) of diethyl oxalate were introduced under a stream of argon into a four-necked reaction flask fitted with a reflux condenser. The suspension was heated with an oil bath at 90°C (internal temperature) for 9 hours. The triethylamine was removed by rotary evaporation under a reduced pressure of 20 mbar (2 kPa) at 60°C. A sample was removed and analysed by GC at the end of this first reaction step to investigate the formation of the intermediate EOA and product EOAE. The mixture was then heated in a second reaction step at 135°C (internal

temperature) for an additional 9 hours. Ethanol and water were removed and a second GC analysis was performed at the end of the reaction. EOAE was identified as the major product. The GC analysis established a 16.66 w/w % amount of EOAE and a 7.72 w/w % amount of EOA. The overall yield EOAE + EOA in this two-step, one-pot process, based on the employed amount of alanine, was 69.4%.

Example 9

5.93 g (66 mmol) of alanine followed by 28.35 g (35 ml, 80 mmol, 1.2 equivalents) of high boiling trioctylamine of density 0.811 g/l and finally 39.9 g (37 ml, 264 mmol, 4 equivalents) of diethyl oxalate were introduced under a stream of argon into a four-necked reaction flask fitted with a reflux condenser. The reaction mixture was heated with an oil bath at 90°C (internal temperature) for 9 hours. Then the mixture was heated in a second reaction step at 135°C (internal temperature) for an additional 9 hours. Two phases formed when the reaction mixture was cooled to 25°C. The crude organic products, including EOAE and EOA, were contained in the lower phase and were separated from the trioctylamine using a separating funnel. GC analysis of the crude product after removal of ethanol and water indicated that diethyl oxalate remained in the product mixture. The GC analysis indicated a 12.43 w/w % amount of EOAE and a 8.97 w/w % amount of EOA. The overall yield EOAE + EOA in this two-step, one-pot process, based on the employed amount of alanine, was 79.3%.

Example 10

Into a four-necked reaction flask fitted with a reflux condenser were introduced under a stream of argon 2.96 g (33 mmol) of alanine followed by 4.04 g (5.55 ml, 40 mmol, 1.2 equivalents) of triethylamine and finally 23 g (132 mmol, 4 equivalents) of dipropyl oxalate. The resulting suspension was heated with an oil bath at 90°C (internal temperature) for 9 hours. The mixture was then heated at 135°C for an additional 9 hours. Propanol and water were removed at reduced pressure and a yellow oil containing the desired product propyl N-propoxalyl-alaninate was isolated (total mass of the final crude product mixture: 21.83 g). 10 g of this crude product were purified by column chromatography (100 g silica gel; hexane/ethyl acetate 80 : 20 v/v). After removal of the solvent by evaporation under reduced pressure, 2.32 g of a colourless oil were isolated and analysed.

Analysis:

R_f (silica gel, hexane/ethyl acetate 80/20) = 0.20;

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.85 (t, J = 7.5 Hz, 3H, -CH_3), 0.90 (t, J = 6 Hz, 3H, -CH_3), 1.40 [d, J = 6 Hz, 3H, CH_3 (Ala)], 1.6 (St, J = 6 Hz, 2H, O-CH_2-CH_2-CH_3), 1.7 (St, J = 9 Hz, 2H, O-CH_2-CH_2-CH_3), 4.10 (t, J = 6 Hz, 2H, O-CH_2), 4.20 (t, J = 7.5 Hz, 2H, O-CH_2), 4.55 (p, J = 7.5 Hz, 1H, -aH), 7.60 (bs, J = 6 Hz, 1H, NH);

^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 171.8, 160.2, 155.9, 68.6, 67.3, 48.6, 21.8, 21.7, 18.1, 10.2, 10.1;

IR (MIR): n = 3357, 1737, 1696, 1190 cm^{-1};

Mass spectroscopy (EI): m/z = 246.3 (M+ H^+), 263.2 (M+ NH_4^+);

Elemental analysis: $C_{11}H_{19}NO_5$, calculated: C 53.87, H 7.81, N 5.71%; found: C 53.95, H 7.97, N 5.78%.

Example 11

5.93 g (66 mmol) of alanine followed by 8.08 g (11.15 ml, 80 mmol, 1.2 equivalents) of triethylamine and finally 53.4 g (54 ml, 264 mmol, 4 equivalents) of dibutyl oxalate were introduced under a stream of argon into a four-necked reaction flask fitted with a reflux condenser. The resulting suspension was heated for 8 hours at 95°C (internal temperature). The mixture was then heated for 15 hours at 135°C in order to obtain the maximum amount of butyl N-butoxalyl-alaninate. Butanol and water were removed by rotary evaporation which yielded a yellow oil (total mass of the final crude product mixture: 45.19 g). 10 g of this crude product were purified by column chromatography (100 g silica gel; hexane/ethyl acetate 80 : 20 v/v). After removal of the solvent by evaporation under reduced pressure 1.3 g of a yellow oil was isolated. A second column chromatography was required (100 g silica gel, toluene/ether 70 : 30 v/v) in order to isolate the butyl N-butoxalyl-alaninate. 1.1 g of a colourless oil was isolated and analysed.

Analysis:

R_f (silica gel, hexane/ethyl acetate 80/20) = 0.20;

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.8 (t, J = 2 Hz, 3H, -CH_2-CH_3), 0.90 (t, J = 2 Hz, 3H, -CH_2-CH_3), 1.30 (m, 4H, 2 x CH_2-CH_2-CH_2-CH_3), 1.40 [d, J = 6 Hz, 3H, -CH_3 (Ala)], 1.55 (p, J = 7.5 Hz, 2H, O-CH_2-CH_2-CH_2-CH_3), 1.65 (p, J = 7.5 Hz, 2H, O-CH_2-CH_2-CH_2-CH_3), 4.10 (t, J = 6 Hz, 2H, O-CH_2), 4.20 (t, J = 7.5 Hz, 2H, O-CH_2), 4.50 (p, J = 7.5 Hz, 1H, -aH), 7.60 (bs, J = 9 Hz, 1H, NH);

^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 171.8, 160.2, 155.9, 67, 65.6, 48.6, 30.4, 30.3, 19, 18.9, 18, 13.6, 13.5;

IR (MIR): n = 3349, 1738, 1524, 1204 cm^{-1};

Mass spectroscopy (EI): m/z = 274.2 (M+ H^+), 291.3 (M+ NH_4^+);

Elemental analysis: $C_{13}H_{23}NO_5$, calculated: C 57.13, H 8.48, N 5.12%; found: C 56.98, H 8.63, N 5.09%.

Example 12

5.93 g (66 mmol) of alanine followed by 8.08 g (11.15 ml, 80 mmol, 1.2 equivalents) of triethylamine and finally 31 g (264 mmol, 4 equivalents) of dimethyl oxalate were introduced under a stream of argon into a four-necked reaction flask fitted with a reflux condenser. The resulting suspension was heated for 8 hours at 95°C (internal temperature). The duration of the second heating step was decreased because of decomposition of the crude product. The mixture was thus heated for 6 hours at 135°C in order to obtain the maximum amount of methyl N-methoxalyl-alaninate. Methanol and water were removed by rotary evaporation which yielded a yellow oil (total mass of the final crude product mixture: 23.23 g). 10 g of crude product were purified by column chromatography (100 g silica gel, hexane/ethyl acetate 80 : 20 v/v). The non-polar dimethyl oxalate was easily separated in the leading fractions and the product was obtained: 2.58 g of a colourless oil. After storage for 3 days at room temperature solids appeared in the colourless oil. A Kugelrohr distillation [40-80°C, 50 mbar (5 kPa)] was performed and the white solid was removed and 1.53 g of a colourless oil was isolated as the main product, being methyl N-methoxalyl-alaninate, and analysed.

Analysis:

R_f (silica gel, hexane/ethyl acetate 50/50): = 0.36;

1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.40 [d, J = 9 Hz, 3H, -CH_3 (Ala)], 3.71 (s, 3H, O-CH_3), 3.84 (s, 3H, O-CH_3), 4.55 (p, J = 7 Hz, 1H, -αH), 7.6 (bs, J = 9 Hz, 1H, NH);

^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 172.1, 160.5, 155.6, 53.6, 52.6, 48.5, 17.9;

IR (MIR): n = 3349, 1738, 1524, 1204 cm^{-1};

Mass spectroscopy (EI): m/z = 190.1 (M+H^+), 207.1 (M+ NH_4^+);

Elemental analysis: $C_7H_{11}NO_5$, calculated: C 44.45, H 5.86, N 7.40%; found: C 44.12, H 5.76, N 7.36%

Example 13

Into a double-jacketed, 4-necked 500 ml glass reactor equipped with a circulation thermostatic temperature control, an overhead stirrer with propeller, a thermometer/ controller, a dephlegmator (partial condensation head), a reflux cooler, a vacuum system, cold traps and argon degassing means were introduced under an argon atmosphere 78.9 g (0.9 mmol) of L-alanine in 258.4 g (1.8 mol, 2 equivalents) of diethyl oxalate. The mixture was stirred at 300 rpm and was heated for 40 minutes up to an internal temperature of 135°C (mantle temperature 140°C). At the start of the reaction the dephlegmator was set to 100°C. The ethanol and further low-boiling constituents were continuously removed from the reaction mixture in a stream of argon over the dephlegmator into a prefraction collecting flask. The reaction mixture was heated for a further 8 hours 10 minutes at the same temperature, during which period the alanine became completely dissolved. After changing the collecting flask the dephlegmator was heated to 110°C (mantle temperature 110°C). The unreacted excess diethyl oxalate was distilled off from the reaction products at an initial internal temperature of 119°C/mantle temperature of 140°C/ reduced pressure of 55 mbar (5.5 kPa) and a final internal temperature of 133°C/mantle temperature of 140°C/reduced pressure of 20 mbar (2 kPa) via the dephlegmator within about 35 minutes.

The resulting mixture containing the crude desired product was cooled to room temperature (becoming viscous) and analyzed by GC, and found to contain 63.3 w/w % of EOA and 15.8 w/w % of EOAE (the yield based on alanine totalled 79.1%).

Example 14

Into a double-jacketed, 4-necked 500 ml glass reactor equipped with a circulation thermostatic temperature control, an overhead stirrer with propeller, a thermometer /controller, a dephlegmator (partial condensation head), a reflux cooler, a vacuum system, cold traps and argon degassing means were introduced at room temperature under an argon atmosphere 160 g of a reaction mixture of EOA and EOAE dissolved in 200 ml of demineralized water. The aqueous solution was extracted three times with a total of 300 ml of toluene at room temperature, and the combined aqueous phases stirred in the reactor at 18°C for about 16 hours. The resulting pale yellow crystals were filtered off and then dissolved in 500 ml of ethyl acetate in an Erlenmeyer flask, and the solution dried over 40 g of anhydrous sodium sulphate. Subsequently the solution was concentrated under reduced pressure using a rotary evaporator and the residue dissolved, still in the rotary evaporator, in 200 ml of diethyl ether at an internal temperature of 30°C. After being stirred for two hours at an internal temperature of about 1-2°C the solution contained crystals, which

were then filtered off, washed with diethyl ether at -5°C and dried in a drying oven for about 16 hours at about 40°C under a reduced pressure of 20 mbar (2 kPa). In this manner 18.7 g of EOA were obtained in crystalline form.